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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/920,902	08/03/2001	Amine Abina	065691-0246	9796

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EXAMINER
WEHBE, ANNE MARIE SABRINA

ART UNIT	PAPER NUMBER
1632	14

DATE MAILED: 06/03/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/920,902	Abina
Examiner	**Art Unit**
Anne Marie Wehbé	1632

-- *The MAILING DATE of this communication appears on the cover sheet with the correspondence address* --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) [X] Responsive to communication(s) filed on *Mar 28, 2003* .

2a) [X] This action is **FINAL**. 2b) [ ] This action is non-final.

3) [ ] Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) [X] Claim(s) *1-88* is/are pending in the application.

4a) Of the above, claim(s) *17, 18, 23-26, 28, 31-42, and 48* is/are withdrawn from consideration.

5) [ ] Claim(s) _____ is/are allowed.

6) [X] Claim(s) *1-16, 19-22, 27, 29, 30, 43-47, and 49-88* is/are rejected.

7) [ ] Claim(s) _____ is/are objected to.

8) [ ] Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) [ ] The specification is objected to by the Examiner.

10) [ ] The drawing(s) filed on _____ is/are a) [ ] accepted or b) [ ] objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) [ ] The proposed drawing correction filed on _____ is: a) [ ] approved b) [ ] disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) [ ] The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) [ ] Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) [ ] All b) [ ] Some* c) [ ] None of:

1. [ ] Certified copies of the priority documents have been received.
2. [ ] Certified copies of the priority documents have been received in Application No. _____ .
3. [ ] Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) [ ] Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) [ ] The translation of the foreign language provisional application has been received.

15) [ ] Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) [ ] Notice of References Cited (PTO-892)
2) [ ] Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) [ ] Information Disclosure Statement(s) (PTO-1449) Paper No(s). ____
4) [ ] Interview Summary (PTO-413) Paper No(s). ____
5) [ ] Notice of Informal Patent Application (PTO-152)
6) [ ] Other:

DETAILED ACTION

Applicant's amendment and response received on 3/28/03 has been entered. New claims 49-88 have been added. Claims 1-88 are now pending in the instant application. This application contains claims 17-18, 23-26, 28, 31-42, and 48 drawn to an invention nonelected with traverse in Paper No. 9. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144). See MPEP § 821.01. Claims 1-16, 19-22, 27, 29-30, 43-47, and 49-88 are currently under examination. It is further noted that claims 1-16, 19-22, 27, 29-30, and 43-47 have not been amended to reflect the elected invention which is the subject matter of Group I, the administration of nucleic acids encoding heterologous proteins. The indicated claims continue to encompass protein administration, a non-elected invention. The applicant is advised, as in the previous office action, that claims 1-16, 19-22, 27, 29-30, and 43-47 are only subject to examination to the extent they encompass the elected subject matter. In regards to all claims currently under examination, claims 1-16, 19-22, 27, 29-30, 43-47, and 49-88, the applicant is further reminded of their election for examination of the species "viruses" for agents recited in the instant claims. An action on the merits follows.

The examiner of record and art unit for this application have changed, see page 13.

Those sections of Title 35, US code, not included in this action can be found in the previous office action.

Claim Objections

The objections to claims 5, 11, 14-16, 19-22, and 43-45 under 37 CFR 1.75(c) are withdrawn in view of applicant's claim amendments.

New claims 62 and 63 are objected to under 37 CFR 1.75(c), as being of improper dependent form. MPEP 608.019(n). The claims depend on multiple parent claims and fail to refer to those parent claims in the alternative.

Claim Rejections - 35 USC § 101

The rejection of claims 27 and 43-45 under 35 U.S.C. 101 has been withdrawn in view of applicant's amendments to the claims.

Claim Rejections - 35 USC § 112, second paragraph

The rejection of claims 1-11, 27, 29-30 and 43-47 under 35 U.S.C. 112, second paragraph, for indefiniteness is maintained. Applicant's arguments have been fully considered but

have not been found persuasive in overcoming the instant grounds of rejection for reasons of record as discussed in detail below.

The applicant argues that the election of a species is only for search purposes and as the elected species is free of the prior art, the office is required to extend the search. However, claims 1-11, 27, 29-30, and 43-47 were rejected based on the fact that these claims continue to recite subject matter directed to a non-elected **invention**, or to depend upon claims which are non-elected based on restriction between separately patentable **inventions**. The election of species requirement was made between various species of "agent". The previous office action clearly stated that the recited claims were rejected based on their recitation of a non-elected invention, the administration of heterologous protein, see page 12 of the previous office action. The restriction, made final in paper no. 10, between administration of a heterologous protein and administration of a nucleic acid encoding a heterologous protein was based on the fact that the administration of proteins and the administration of nucleic acids are considered distinct and separately patentable inventions. Thus, applicant's arguments regarding election of species is not applicable to the instant grounds of rejection.

Furthermore, the applicant is advised that regarding the election of the species "viruses", although the elected species of agent "viruses" appears to be free of the prior art of record, the elected species and the genus of agents as a whole are currently rejected under 35 U.S.C. 112, for lack of enablement. MPEP 809.029(a) clearly states that only upon an indication that a generic claim is found allowable will the applicants be entitled to consideration of claims to additional

species which are written in dependant form. Claims which recite the genus "agent" have not been found to be allowable as they are rejected under 35 U.S.C. 112, first paragraph, for lack of enablement.

The rejection of claims 4, 13-16, and 19-22 under 35 U.S.C. 112, second paragraph, for indefiniteness regarding "fragments thereof" is withdrawn in view of applicant's argument.

The rejection of claims 6 and 19-22 under 35 U.S.C. 112, second paragraph, for indefiniteness regarding "prior said" is withdrawn in view of applicant's amendment.

The rejection of claims 8, 12-16, and 19-22 under 35 U.S.C. 112, second paragraph, for indefiniteness regarding "which comprising" is withdrawn in view of applicant's amendment

The rejection of claims 9-16 and 19-22 under 35 U.S.C. 112, second paragraph, for indefiniteness regarding "regulation sequences" is withdrawn in view of applicant's amendment

The rejection of claims 13-16 and 19-22 under 35 U.S.C. 112, second paragraph, for indefiniteness regarding "which not expressing" is withdrawn in view of applicant's amendment

The rejection of claims 20 and 22 under 35 U.S.C. 112, second paragraph, for indefiniteness regarding "fragments thereof" is withdrawn in view of applicant's arguments.

The rejection of claims 21-22 and 29-30, and the rejection of claims 27 and 43-45 under 35 U.S.C. 112, second paragraph for lack of antecedent basis are withdrawn in view of applicant's amendments to the claims.

The rejection of claim 29 under 35 U.S.C. 112, second paragraph, for indefiniteness of "ethiology" is withdrawn in view of applicant's amendment.

The rejection of claims 30 and 43-47 under 35 U.S.C. 112, second paragraph for indefiniteness of "chosen among" or "selected among" is withdrawn in view of applicant's amendment.

The rejection of claim 30 under 35 U.S.C. 112, second paragraph for indefiniteness of "parasites infections" is withdrawn in view of applicant's amendment.

The rejection of claim 47 under 35 U.S.C. 112, second paragraph for indefiniteness of "intradermic injection" is withdrawn in view of applicant's amendment

Claim Rejections - 35 USC § 112, first paragraph

Original, amended, or new claims 1-16, 19-22, 27, 29-30, 43-47, and 49-88 stand rejected under 35 U.S.C. 112, first paragraph, for lack of enablement. Applicant's arguments and exhibits A and B have been fully considered but have not been found persuasive in overcoming the instant grounds of rejection for reasons of record as discussed in detail below.

The applicant argues that the specification provides a working example using recombinant adenovirus encoding huTPO which when administered at a "tolerizing" dose results in an apparent decrease in the amount of anti-huTPO antibody in the host, and that, "[a]s long as the specification discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim, then the enablement requirement of 35 U.S.C. 112 is satisfied", taken from the MPEP, section 2164.01 which in turn cites *In re Fisher*. The applicant further cites *Spectra-Physics, Inc. v. Coherent, Inc.* for stating that, "[f]ailure to disclose other methods by which the claimed invention may be made does not render a claim invalid. In response office explained in detail why the disclosure provided by the specification, including the working example, does not in fact bear a reasonable correlation to the scope of the claims. analyzed the specification in direct accordance to the factors outlined in *In re Wands*, namely 1) the nature of the invention, 2) the state of the prior art, 3) the predictability of the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the quantity of experimentation necessary, 7) the relative skill of the skilled artisan, and 8) the

breadth of the claims, and presented detailed scientific reasons supported by publications from the prior art for the finding of a lack of enablement for the scope of the instant methods. Please note that establishing a *prima facie* case for non-enablement requires consideration of many factors, not just the amount of disclosure present in the specification. Note as well that case law including the Marzocchi decision sanctions both the use of sound scientific reasoning and printed publications to support a holding of non-enablement (see *In re Marzocchi* 169 USPQ 367, and *Ex parte Sudilovsky* 21 USPQ2d 1702). Further, the unpredictability of a particular art area may alone provide reasonable doubt as to the accuracy of the broad statement made in support of enablement of claims. See *Ex parte Singh*, 17 USPQ2d 1714 (BPAI 1991). Of particular relevance to the instant case, 35 U.S.C. 112 also requires that the scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art, and that the specification must teach those of skill in the art how to make and how to use the invention as broadly claimed. *In re Goodman*, 29 USPQ2d at 2013 (Fed. Cir. 1994), citing *In re Vaeck*, 20 USPQ2d at 1445 (Fed. Cir. 1991), and *In re Fisher*, 166 USPQ 18, 24 (CCPA 1970). Ultimately, case law states that ".. the disclosure of an application shall inform those skilled in the art how to use applicant's alleged discovery, not to find out how to use it for themselves." *In re Gardner* 166 USPQ 138 (CCPA) 1970.

Furthermore, in applications directed to inventions in arts where the results are unpredictable, such as gene therapy, the disclosure of a single species usually does not provide an adequate basis to support generic claims. *In re Soll*, 97 F.2d 623, 38 USPQ 189 (CCPA 1938). In

cases involving unpredictable factors, such as most chemical reactions and physiological activity, more may be required. *In re Fisher*, 166 USPQ 18 (CCPA 1970) (contrasting mechanical and electrical elements with chemical reactions and physiological activity). See also *In re Wright*, 999 F.2d 1557, 27 USPQ2d 1510 (Fed. Cir. 1993); *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). This is because it is not obvious from the disclosure of one species, what other species will work. *In re Dreshfield*, 110 F.2d 235, 45 USPQ 36 (CCPA 1940), gives this general rule: "It is well settled that in cases involving chemicals and chemical compounds, which differ radically in their properties it must appear in an applicant's specification either by the enumeration of a sufficient number of the members of a group or by other appropriate language, that the chemicals or chemical combinations included in the claims are capable of accomplishing the desired result." In the instant case, the applicants specification is directed primarily towards the use of adenovirus as the "agent" for decreasing neutralizing antibodies against the heterologous protein, whereas the claims broadly recite the genus of "viruses". While the specification does state that other viruses may be used, including adeno-associated virus, retrovirus, or pox virus, the substantial differences between these viruses and adenoviruses were well known at the time of filing, including differences in tropism, infectivity, pathogenicity, structure, and function. Based on the substantial differences between species of viruses, the skilled artisan would have considered a correlation between the activity of adenovirus *in vivo* and other non-adenoviruses as unpredictable. Please note that applicant's statement that the publications by Drake et al., Braun et al., Lapointe et al., Havenga et al., Mercier et al., and Esslinger et al. demonstrate viruses

which work in the same way as adenovirus could not be evaluated as none of these references were provided for the examiner's consideration and the response does not describe in any detail the particular teachings of any of these references.

The applicant further argues that the methods of the invention may be performed with any secreted membrane protein, citing as evidence papers by Wucherpfunnig et al., Zhao et al., Levin et al., and Panaoutsakopoulou et al.. These references were provided as exhibit A. It is unclear from this statement by applicant's representative whether the applicant means that any secreted membrane protein can be used as the "agent" in the instant methods, or as the "heterologous protein" in the instant methods. The references provided do not clarify this issue. The references provided discuss the relationship between viruses and the onset or exacerbation of autoimmune diseases by molecular mimicry. These references do not appear to be on point in regards to the claims under examination and the rejection of record. The subject under examination is drawn to methods of inhibiting the formation of neutralizing antibodies against a heterologous protein by co-administering an "agent" such as an adenovirus and a nucleic acid encoding a heterologous protein. The references provided show that viruses may be capable of causing or exacerbating autoimmunity, and do not teach or suggest using viruses to inhibit neutralizing antibody formation.

The applicant also argues that recent gene therapy studies in humans show that gene therapy can produce clinical benefits, citing Kay et al., Abonour et al., Ge et al., Gallo-Penn et al., Hacein-Bey-Abina et al., and Aiuti et al., provided as exhibit B. Kay et al. does not support

applicant's position that gene therapy was considered predictable at the time of filing. Kay et al., while demonstrating some expression of factor IX in haemophilia B patients treated with an AAV vector, concludes only that these results indicate that AAV-mediated gene therapy may have the potential to demonstrate efficacy against haemophilia B (Kay et al., page 260, column 1). Kay in fact states that, "[t]esting at higher doses will be required to confirm this interpretation", and that, "[t]he record so far has been discouraging, with no clear-cut evidence or success with in vivo gene therapy" (Kay et al., page 260, column 1). Thus, Kay et al. actually supports the position of the Office that gene therapy of disease is considered unpredictable. Abounour et al.. also not support applicant's position. The reference teaches *ex vivo* methods of transducing cells with virus and reintroducing the cells back into the host. *Ex vivo* gene therapy is substantially different from applicant's methods of introducing virus directly *in vivo*. Further, Abounour et al. provides no evidence of any clinical benefit for the transduced cells versus the untransduced cells. In regards to Hacein-Bey-Abina et al. and Aiuti et al., both references teach *ex vivo* protocols and were published after the filing date of the instant application. The applicant is reminded that enablement is determined based on the state of the art at the time of filing, *In re Glass*. Finally, both Ge et al. and Gallo-Penn et al. support the Office's position that anti-viral immune responses were known to be a significant problem affecting the use of viral vectors for gene therapy at the time of filing. Neither of these references teach that viruses can in fact be used to prevent the formation of neutralizing antibodies.

Therefore, while applicant's arguments and supporting references have been considered, they do not overcome the rejection of record, see paper no. 10 for a detailed presentation of the instant grounds of rejection. The rejection of record is maintained.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication from the examiner should be directed to Anne Marie S. Wehbé, Ph.D., whose telephone number is (703) 306-9156. The examiner can be reached Mon-Fri from 10:30-7:00 EST. If the examiner is not available, the examiner's supervisor, Deborah Reynolds, can be reached at (703) 305-4051. General inquiries should be

directed to the group receptionist whose phone number is (703) 308-0196. The technology center fax number is (703) 308-4242, the examiner's direct fax number is (703) 746-7024.

Dr. A.M.S. Wehbé

ANNE M. WEHBE PH.D
PRIMARY EXAMINER